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Rewriting the playbook for clinical testing in a rare disease

A Novartis team blazes new trails with an experimental treatment for spinal muscular atrophy.

By Eric Bender | Jul 13, 2015

Spinal muscular atrophy (SMA) is the leading genetic killer of infants and toddlers. Between 1 in 6,000 and 1 in 10,000 infants worldwide are born with the disease, which attacks motor neurons and weakens muscles. There is no cure at this time. Most children born with type 1 SMA, the most extreme form of the disease, do not live to see their second birthdays.

“This horrible disease demands attention,” says Evan Beckman, Global Head of Translational Medicine for the Novartis Institutes for Biomedical Research (NIBR). “To try and help these kids, we’ve taken an unconventional approach to drug development, first testing an experimental treatment in the patients who need it most.”

Novartis recently launched an early clinical trial with a novel design in Europe to test the safety and effectiveness of an investigational drug called LMI070. The compound will be administered to infants with type 1 SMA.

Experimental treatments normally are tested first in healthy adult volunteers and then in adult patients with less severe forms of disease, primarily to look for toxicity and secondarily to get early clues about effectiveness. Drugs developed with infants in mind typically follow a long set of procedures, in which they are tested for toxicity in a series of ever-younger patient groups. Teenagers, for example, generally receive the treatment before it’s administered to younger children.

The Novartis team of clinical experts saw that the traditional trial approach might not provide critical information on the drug’s safety, effectiveness and proper dosage, and that following the standard process would take several years at best, says Beckman.

Instead, the team reasoned, starting clinical testing in infants with type 1 SMA could help to meet the greatest unmet need, and help to benefit those patients in their critical early months when the drug might be most effective.

“We have a molecule that could potentially be effective in preventing the loss of nerves in infants with SMA,” says Ronenn Roubenoff, NIBR’s Head of Translational Medicine for Musculoskeletal Diseases. “We know it works in mice. We know it gets into the brain, the nerves and the muscles. And we think we have a way of delivering it as safely as possible with once-a-week oral dosing.”

The LMI070 trial began in several European countries this spring, and if all goes well, it will continue to treat a total of 10 patients this year. A decision is expected to be made at the beginning of 2016 about whether or not to continue with additional patients.

Boosting protein production

SMA is driven by mutations in a gene called SMN1, which creates a protein known as survival motor neuron (SMN). Another very closely related gene, SMN2, can create the SMN protein and help to reduce SMA's effect, but SMN2 often generates versions of the protein that are not fully formed. Various SMA drug candidates have tried to treat the disease by boosting production of fully-formed SMN protein production from SMN2.

Novartis's LMI070 is a small molecule that is dissolved in liquid to be taken relatively easily, even by infants. In pre-clinical research, including tests with very young animal models, the compound gave encouraging results for effectiveness and safety. Importantly, Novartis scientists also have discovered how it works at the molecular level.

In a clinical study of an experimental treatment for SMA, investigators must measure the amount of the SMN protein to see if the drug is working, Roubenoff notes. Healthy volunteers produce all the SMN protein they need, so they can't provide that readout. Nor would they derive any benefit from the compound, which carries risks. Adults with less severe forms of SMA might produce around 80% of normal levels of the protein, so that the effects of the drug might be hard to assess in that group as well.

"We need to test this compound in infants with the most severe form of the disease to see if it works," he says. "These patients need treatment options. Currently, the only thing doctors can do is provide feeding tubes when the infant cannot swallow enough food and a ventilator when the infant can no longer breathe without assistance. This does prolong life, but it doesn't treat the underlying disease or provide much quality of life."

Since the normal downhill course of type 1 SMA is well known, the trial will not use a placebo control group of patients. Additionally, both the natural history of the disease and evidence from animal models suggest that there is a critical window of time in the first months after birth to try to counteract the disease—the earlier the treatment, the better the chances of preserving nerves.

This trial approach was inspired by cancer clinical studies, which also tend to bypass the step of healthy volunteers. In both cases, the severity of the disease drives the unconventional clinical research strategy.

"This project is very important to us," says Evan Beckman. "We're committed to advancing a treatment for these young patients and their families."

Learn about work with the SMA Foundation that accelerated the discovery of this experimental treatment.

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